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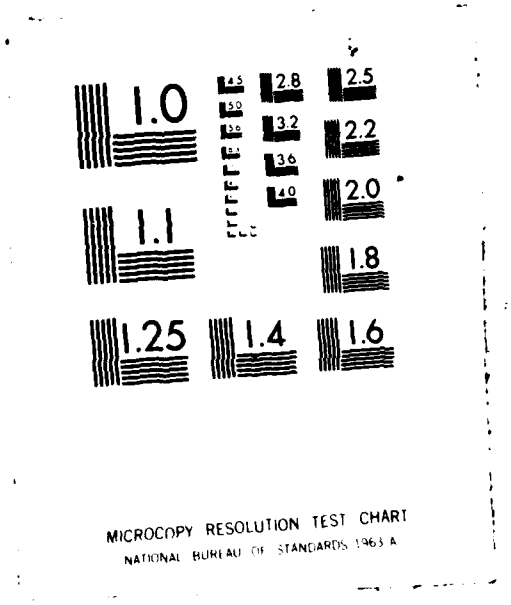
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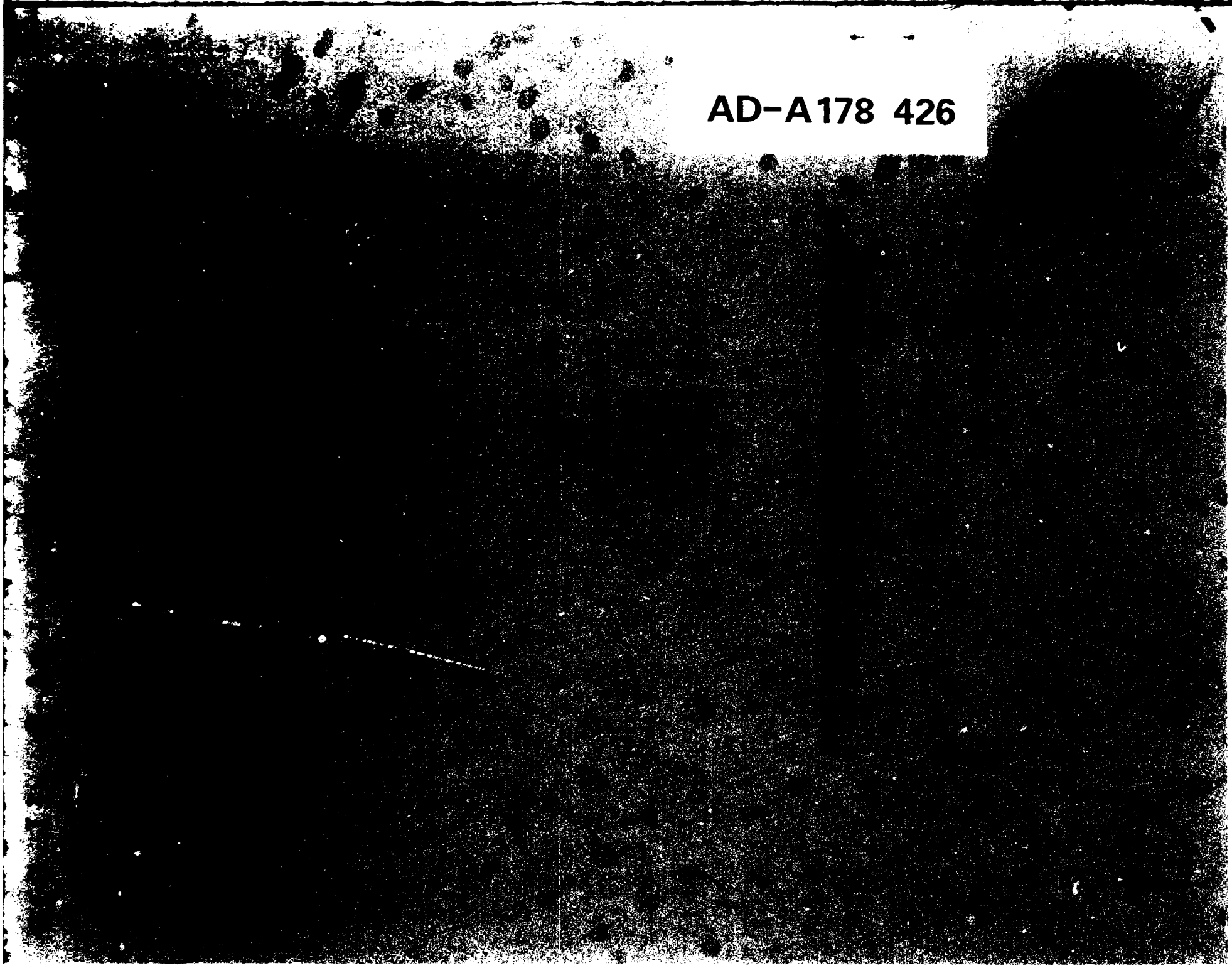
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Plasma and erythrocyte acetylcholinesterase (AChE) activity changes in response to hemorrhage were studied in two groups of conscious immature swine (21 ± 1 kg) 7 to 10 days after chronic implantation of arterial and venous catheters. One group (n=10) was immobilized in a Pavlov sling, the other (n=6) remained unrestrained in portable holding cages. The animals were hemorrhaged 36 ml/kg over 60 minutes and studied over another 120 minutes. Compared to unrestrained pigs, animals in the sling showed less of a decline

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in mean arterial blood pressure (37 ± 3 vs 61 ± 11 mmHg) at the end of hemorrhage and a more marked increase in heart rate (201 ± 17 vs 133 ± 12 beats/min); these group differences were significant (~~P<0.05~~). In both groups hematocrit was reduced significantly to the same level, and arterial blood gases showed no differences. Erythrocyte AChE activity also showed no difference between groups or significant change during hemorrhage. Plasma AChE activity fell significantly during hemorrhage, from 0.41 ± 0.04 to 0.35 ± 0.03 U/ml in the sling animals and from 0.50 ± 0.02 to 0.04 ± 0.02 U/ml in the caged animals/ The ~~between-group~~ difference was not statistically significant. The decrease in plasma AChE activity persisted for over two hours after hemorrhage. Following hemorrhage there was a 57% reduction in total intravascular AChE activity and an 18% reduction in total plasma activity. Although immobilization altered cardiovascular variables, it did not modify AChE activity. The reduction of AChE activity following hemorrhage may increase susceptibility to anesthetic agents.

Abstract

Plasma and erythrocyte acetylcholinesterase (AChE) activity changes in response to hemorrhage were studied in two groups of conscious immature swine (21 ± 1 kg) 7 to 10 days after chronic implantation of arterial and venous catheters. One group (n=10) was immobilized in a Pavlov sling, the other (n=6) remained unrestrained in portable holding cages. The animals were hemorrhaged 36 ml/kg over 60 minutes and studied over another 120 minutes. Compared to unrestrained pigs, animals in the sling showed less of a decline in mean arterial blood pressure (37 ± 3 vs 61 ± 11 mmHg) at the end of hemorrhage and a more marked increase in heart rate (201 ± 17 vs 133 ± 12 beats/min); these group differences were significant ($P<0.05$). In both groups hematocrit was reduced significantly to the same level, and arterial blood gases showed no differences. Erythrocyte AChE activity also showed no difference between groups or significant change during hemorrhage. Plasma AChE activity fell significantly during hemorrhage from 0.41 ± 0.04 to 0.35 ± 0.03 U/ml in the sling animals and from 0.50 ± 0.02 to 0.04 ± 0.02 U/ml in the caged animals. The between-group difference was not statistically significant. The decrease in plasma AChE activity persisted for over two hours after hemorrhage. Following hemorrhage there was a 57% reduction in total intravascular AChE activity and an 18% reduction in total plasma activity. Although immobilization altered cardiovascular variables, it did not modify AChE activity. The reduction of AChE activity following hemorrhage may increase susceptibility to anesthetic agents.

Introduction (u)

(u) Acetylcholinesterase (AChE) is responsible for the hydrolysis of the parasympathetic neurotransmitter acetylcholine resulting in inactivation (1). Acetylcholine is important in homeostatic mechanisms that are not under voluntary control and that normally function below the level of consciousness. Inhibition of AChE, such as that resulting from exposure to organophosphates (nerve agents), extends the activity of acetylcholine (2-4), which can be extremely toxic and result in death.

(u) AChE activity is purported to be increased by "stress" (5,6) and to modulate cardiovascular and endocrine responses (6-8). However, Assur and Ermakov (9) noted a markedly reduced plasma and erythrocyte AChE activity during acute blood loss in rats. Bazarevich et al. (10) also noted an initial fall in plasma AChE activity during hemorrhage in rats, with a subsequent rise late in hemorrhage "agony." Others (5, 11-15) have reported changes in AChE activity during trauma and immobilization.

(u) In conventional land warfare a high incidence of acute hemorrhage occurs in the wounded (16-18). An understanding of the response of AChE to hemorrhage will assist in the treatment of wounded soldiers exposed to nerve agents or given nerve-agent antidotes. In the present study the response of plasma and erythrocyte AChE activity during hemorrhage was evaluated in conscious pigs. Two groups of animals were compared to investigate the role of physical restraint (stress) on AChE activity during hemorrhage.

Methods (u)

(u) Sixteen immature (2- to 3-month-old) Duroc swine were studied. The animals were purchased from a commercial supplier and housed in the Institute for at least ten days prior to surgery. They were fed a commercial ration (Purina) and allowed water ad libitum.

(u) After fasting overnight each animal was given a preanesthetic intramuscular injection of 0.08 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was induced using a face mask and maintained with an endotracheal tube. The posterior aorta and external jugular vein were catheterized using sterile procedures. The posterior aorta catheter was tunneled under the skin and exited on the dorsal surface of the back. The external jugular vein catheter was tunneled under the skin and exited on the dorsal surface of the neck. The animal was observed until fully recovered and returned to a holding cage. Catheter patency was maintained by flushing at 3- to 4-day intervals with heparin (1000 U/ml) in normal saline.

(u) After 5 to 7 days of postoperative recovery the animals were fasted overnight. The following morning the animal was transported to the laboratory in a portable holding cage. The pig was allowed to remain in the holding cage (n=6) (105 x 60 cm), or placed into a modified Pavlov sling (n=10). The animal was then connected to a 12-inch pressure-monitoring injection line that had been fitted with a three-way stopcock and filled with heparinized saline. The system was then flushed with heparinized saline and connected to a pressure transducer and monitoring system (Gould Model 24005, Cleveland, OH). Following a 30-minute equilibration period, the animal was hemorrhaged at 36 ml/kg, 50% of the estimated blood volume, in a logarithmic fashion over a 60-minute period. Upon completion of the hemorrhage additional measurements and blood samples were obtained. Reported are the 0-, 60-, 120-, and 180-minute values for the various cardiovascular and biochemical variables during the two types of restraint. Hemorrhage was performed between 0 and 60 minutes following the 30-minute equilibration period. Additionally, plasma and erythrocyte acetylcholinesterase values were measured at 0, 2, 5, 10, 20, 40, 60, 62, 65, 75, 90, 105, 120, 180, and 240 minutes in the animals studied in the holding cage.

(u) Blood pressure, heart rate, and pulse pressure were measured for one minute during each sampling period and an average obtained. Plasma lactate (Sigma Chemical Co., St Louis, MO) and glucose (Beckman Instruments, Anaheim, CA) levels were measured by standard assay techniques. Hematocrit was measured by the microcapillary method. Blood gases were measured (System 1303, Instrumentation Laboratory, Lexington, MA) and base excess values calculated using a nomogram specific for pigs (19). Plasma and red blood cell acetylcholinesterase activities were determined by using a Technicon AutoAnalyzer II system (Technicon, Tarrytown, NY) with slight modification of the method of Ellman et al. (20), with acetylthiocholine as the substrate.

(u) Using a two-way analysis of variance, data were analyzed, and comparisons made between groups and over time. Differences between means were assessed using a Newman-Keuls test. When appropriate, such as to compare body weights between groups, a t-test was used. A probability less than or equal to 0.05 was accepted as being significant. Values in the text are mean plus or minus the standard error of the mean.

Results (u)

(u) There was no significant difference in the body weights (20.8 $\pm$ 1.2 vs 21.1 $\pm$ 0.8 kg) or volume of body removed (734 $\pm$ 43 vs 759 $\pm$ 29 ml) between the two groups of animals. Two of the animals in the sling group died following the completion of hemorrhage, while all of the animals in the cage survived (80 vs 100% survival, $P>0.05$).

(u) A significant reduction in mean arterial pressure occurred with hemorrhage, to a greater degree in control animals (Fig. 1). Pulse pressure was not significantly changed with hemorrhage; however, differences between groups were noted at 120 and 180 minutes (Fig. 1). Although initial heart rates were lower in the sling group, there was an increase during hemorrhage. In the holding-cage animals, no changes in heart rate were noted during hemorrhage (Fig. 1).

(u) The concentration of plasma lactate did not differ between groups during hemorrhage, but after hemorrhage, animals in the sling had reduced levels compared to cage animals (Table I). A similar trend was

noted for glucose but significant differences were not observed (Table I). Hematocrits were reduced in both groups during hemorrhage (Table I). Arterial blood gas measurements are shown in Table II with no difference noted between groups.

(u) Erythrocyte acetylcholinesterase (AChE) activity showed no difference between groups or significant change during the experiment (Fig. 2). However, plasma AChE activity fell during hemorrhage and remained reduced in both groups over the 120 minutes of recovery (Fig. 2). Further analysis of repeated samples for AChE in holding-cage animals showed no change in erythrocyte AChE activity but did show a significant reduction in plasma AChE activity which remained depressed for three hours post hemorrhage (Fig. 3).

Discussion (u)

(u) The variability of responses of AChE activity to various stimuli is not fully understood. Fatranska et al. (5) showed a rapid increase in plasma AChE activity following severe trauma in rats, while repeated trauma of lower intensity produced no change. In humans, however, plasma AChE activity is decreased following burn injury (6,12,13), battlefield trauma (15), and cardiopulmonary bypass surgery (11). These findings suggest that plasma AChE activity is reduced during trauma in humans.

(u) Traumatic conditions have been shown to increase plasma catecholamines. Previously, Kvetnansky et al. (21) found that the increase in AChE activity correlated with elevations in plasma catecholamines. However, Fatranska et al. (5) noted that medullectomy plus sympathectomy lowered basal AChE activity but potentiated the increase in response to immobilization. Thus, while the changes in AChE activity may be associated with changes in plasma catecholamines at times, it appears that the systems can also function independently.

(u) Hemorrhage, while stimulating a rise in catecholamines, results in a reduction in plasma AChE activity (9), except during respiratory disturbance when an increase occurs (10). In the present study physical restraint did not affect the plasma or erythrocyte AChE activities of pigs at rest or during hemorrhage, even though this method of restraint altered cardiovascular and biochemical variables and has been shown by others to elevate plasma catecholamine levels of pigs (22,23).

(u) While erythrocyte AChE activity was unchanged during hemorrhage, plasma AChE activity was reduced. The fall in plasma AChE activity could have been caused by a decrease in acetylcholinesterase synthesis or release from the liver, possibly due to hepatocellular damage during hemorrhage (12). In earlier studies using this hemorrhage model, indices of liver damage were negative (24,25). No change was noted in hepatic blood flow in animals surviving a more severe hemorrhage (26). Thus, alterations in synthesis of AChE in the liver probably do not account for the reduction in plasma activity at the level of hemorrhage used in the present study. The 18% fall in plasma AChE activity could have been caused primarily by transcapillary refill, which may account for as much as 30% of the plasma volume following hemorrhage (27). The sustained reduction of plasma AChE activity for three hours after hemorrhage suggests that AChE is not transferred appreciably from the extravascular to the vascular compartment, and is not rapidly produced and mobilized in response to falls in plasma levels. Of importance is the observation of Frawley et al. (15) that plasma AChE activity may remain at a reduced level for days after a battlefield injury. A fall in plasma AChE activity, however, does not indicate associated changes in autonomic nervous system function, as changes in plasma levels may not reflect changes in AChE at the synaptic cleft.

(u) While no change in erythrocyte AChE activity per milliliter of packed cell volume was found, there was a decrease in the volume of red blood cells due to hemorrhage, reducing the total vascular erythrocyte AChE activity. Using the erythrocyte AChE activities before and after hemorrhage results in a calculated 63% reduction in AChE activity associated with red blood cells due to the red-cell volume being reduced by hemorrhage (Table III). A decrease of 44% in total plasma AChE occurred during hemorrhage. The combined reduction of AChE activity associated with red blood cells and plasma represents a 57% decrease in total vascular AChE activity.

(u) The decrease in available AChE in the vascular compartment is possibly of little consequence since inhibition of up to 90% of activity is necessary to produce abnormal function and AChE is present in most tissue in quantities in excess of that required (1,2). However, the decrease in AChE due to hemorrhage may

explain the finding of Piscevic et al. (28) that simultaneous hemorrhage and chemical trauma resulted in the death of animals exposed to normally nonlethal doses of the nerve agent sarin. Of interest is that in these animals subjected to combined trauma, the clinical symptoms of sarin poisoning (salivation, fibrillation, fasciculations, and convulsions) were not observed or were of "insignificant" intensity. Thus, the decrease in AChE activity which occurs during traumatic hemorrhage may potentiate the responsiveness to acetylcholine.

(u) Assur and Ermakov (9) noted a fall in AChE activity with hemorrhage, which could be rectified in part by using preserved blood that had been stored only briefly. Frawley et al. (15) proposed that the fall in erythrocyte AChE activity in their study of battlefield casualties could in part be explained by a decrease in erythrocyte AChE activity during the storage of blood to be transfused. Further, the respiratory distress during hemorrhage is associated with the fall in AChE activity and may be partially corrected by infusion of exogenous AChE (29). The replacement of AChE activity in resuscitation fluids to be administered following hemorrhage may thus prove beneficial (30).

Conclusion (u)

In conclusion, AChE activity of conscious swine is not altered by physical restraint. Although erythrocyte AChE activity did not change during hemorrhage, plasma AChE activity was reduced, possibly due to dilution occurring because of transcapillary refill. While AChE activities were not dramatically altered by hemorrhage, the vascular AChE content was reduced by over 50%. This reduction in AChE content may increase responsiveness to acetylcholine and cholinergic agents.

Recommendations (u)

1. (u) Further studies of susceptibility to chemical agents following hemorrhage and trauma must be conducted.

2. (u) The efficacy of exogenous AChE administration following hemorrhage should be investigated.

3. (u) The effects of prophylactic treatments and antidotes to chemical agents on the physiological and biochemical responses to hemorrhage and trauma should be investigated.

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TABLE I: Summary of Physiological Values in Hemorrhaged Conscious Swine

	Time (min)			
	0	60	120	180
Hematocrit %				
Cage	27±1	23±2	22±2	22±2
Sling	24±1	23±2	21±2	21±2
Lactate (mg/dl)				
Cage	8.9±0.7	56.2±15.7	52.7±11.3	27.2±8.1
Sling	9.0±1.3	56.2±17.5	26.0±11.1+	12.8±4.1+
Glucose (mg/dl)				
Cage	89±7	141±23	152±20	129±9
Sling	85±6	145±23	127±13	116±11

+ significantly different from cage, $P<0.05$

TABLE II: Summary of Arterial Blood Gas Measurements

	Time (min)			
	0	60	120	180
pH				
Cage	7.43±0.01	7.46±0.02	7.42±0.01	7.44±0.02
Sling	7.40±0.02	7.37±0.06	7.42±0.02	.44±0.03
PO_2 (torr)				
Cage	97.4±3.1	124.2±5.2	107.6±6.0	109.4±6.0
Sling	94.3±3.1	114±4.5	98.6±3.3	99.1±3.3
P_{CO} (torr)				
Cage	37.4±1.1	27.8±1.6	35.8±0.9	35.4±1.0
Sling	37.1±0.9	27.7±1.9	33.0±1.6	34.3±0.9
HCO_3 (mEq/l)				
Cage	25.3±1.1	19.8±0.7	23.4±1.0	24.5±1.3
Sling	22.8±1.7	18.7±1.5	21.7±1.2	23.5±1.2
Base Excess (mEq/l)				
Cage	-6.4±1.0	-10.5±1.3	-8.6±1.2	-6.5±1.4
Sling	-7.8±1.9	-11.9±2.1	-9.3±1.5	-7.5±1.5

TABLE III: Changes In Vascular Content Calculated from the Work of Hannon et al. (27) (American Journal of Physiology 248:R293-R301, 1985) and Based on a 20-kg Pig Hemorrhaged at 38.5 ml/kg.

AChE Activity (u)	Before Hemorrhage	After Hemorrhage
Total Erythrocyte	957	357
Total Plasma	474	263
Total Vascular (Erythrocyte + Plasma)	1431	620

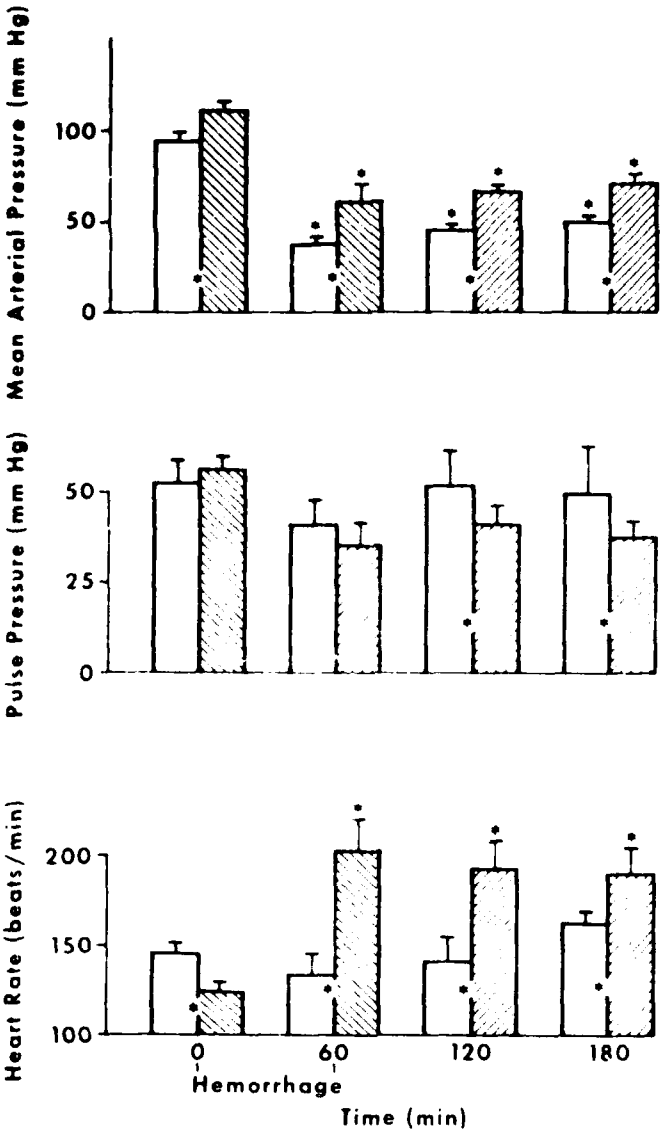

Figure 1: Mean arterial pressure, pulse pressure, and heart rate for surviving animals in the sling (shaded bars) and holding cage (unshaded bars) before and after hemorrhage at 36 ml/kg. An asterisk (*) above the bar indicates that the value is significantly different from the control (time 0) value of that group, $P<0.05$. An asterisk (*) between the bars indicates a significant difference between groups, $P<0.05$.

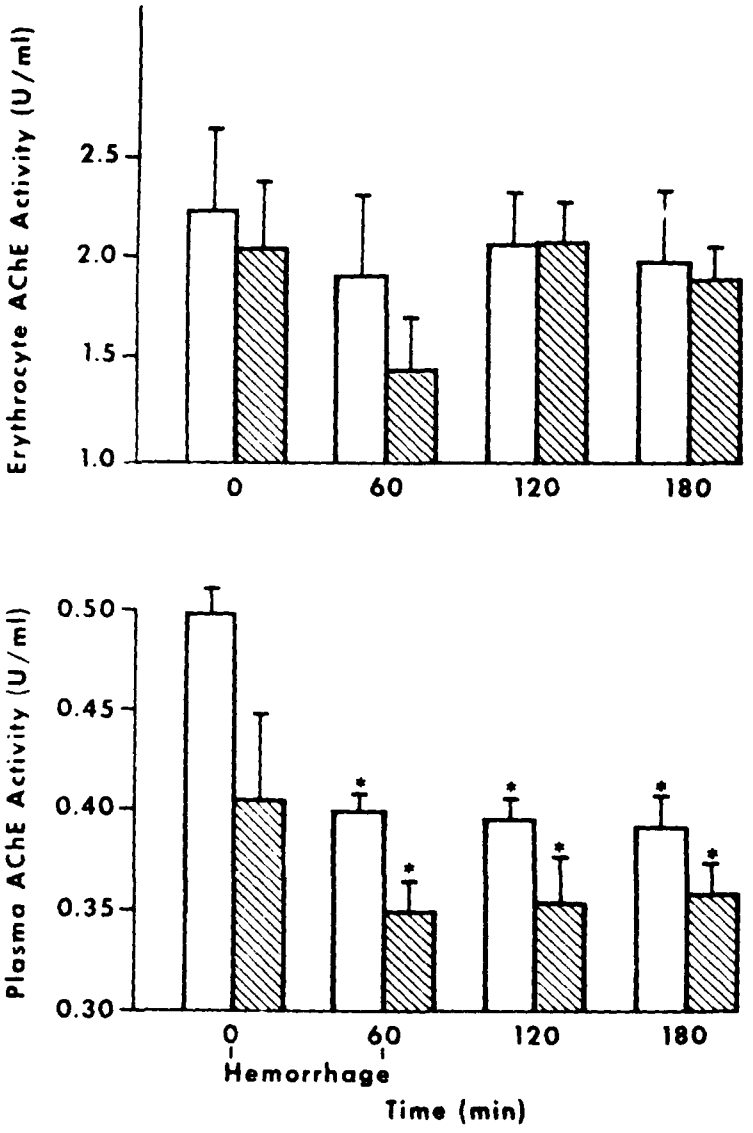

Figure 2: Plasma and erythrocyte acetylcholinesterase (AChE) activity for pigs in a sling (shaded bars) and holding cage (unshaded bars) before and after a 36 ml/kg hemorrhage. An asterisk (*) indicates that the value is significantly different from the time 0 value for that group, $P<0.05$

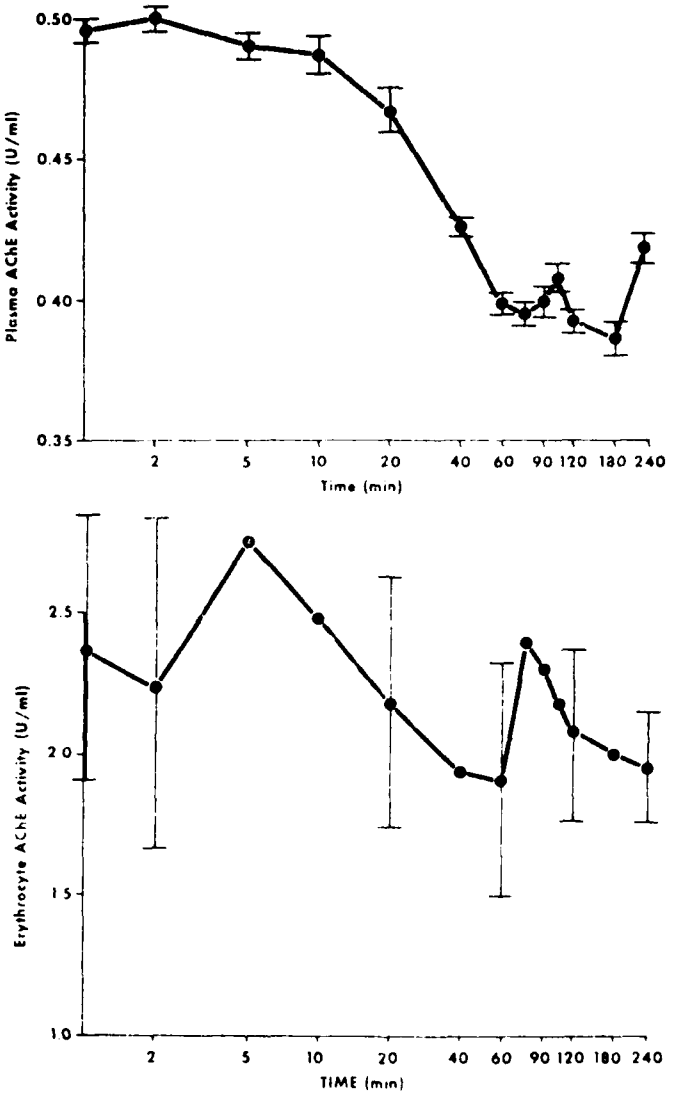

Figure 3: Plasma and erythrocyte acetylcholinesterase (AChE) activity in holding-cage animals during (0-60 min) and following (60-240 min) a 36 ml/kg hemorrhage.

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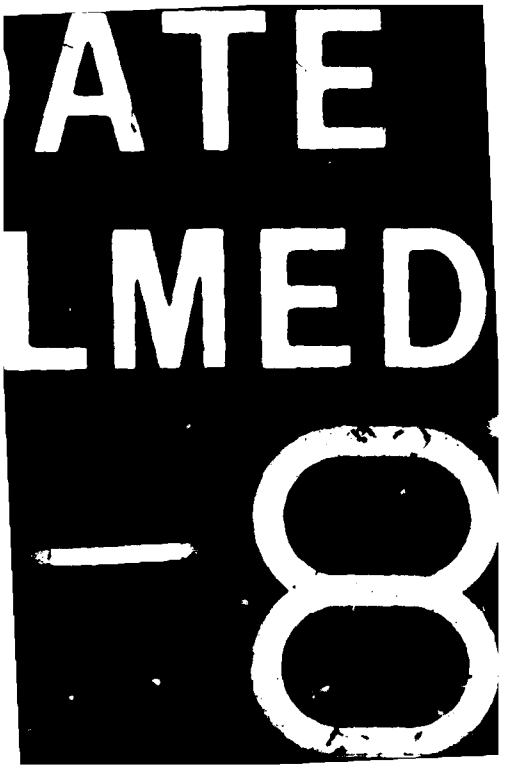
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